

Appln No.: 09/674,191

Amendment Dated: March 12, 2005

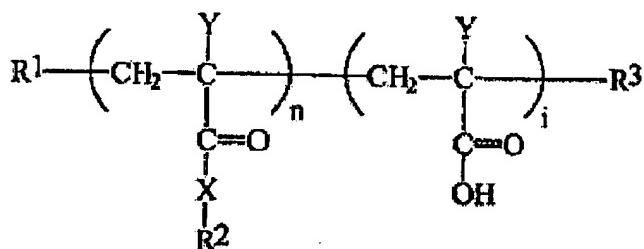
Reply to Office Action of December 16, 2004

**Amendments to the Claims:**

This listing of claims will replace all prior versions, and listings, of claims in the application:

**Listing of Claims:**

1. (currently amended) A compound of the formula



wherein:

R<sup>1</sup> is a member selected from the group consisting of hydrogen, hydroxyl, amino, optionally-substituted alkyl and a ligand;

Y is a member selected from the group consisting of hydrogen, optionally substituted alkyl, optionally-substituted cycloalkyl, optionally-substituted aryl and optionally-substituted heteroaryl;

X is a member selected from the group consisting of optionally-substituted amino, oxygen, sulfur and a carbon single bond;

R<sub>2</sub> is a member selected from the group consisting of hydrogen, C<sub>6</sub>-C<sub>26</sub> alkyl, C<sub>6</sub>-C<sub>26</sub> alkenyl, dialkylglycerolyl, dialkenylglycerolyl, diacylglycerolyl, 1,2-diacyl-sn-glycero-3-phosphoethenyl, 1,2-dialkoxy-3-aminopropanyl and 1,2-diacyloxy-3-aminopropanyl;

R<sup>3</sup> is a member selected from the group consisting of hydrogen, hydroxyl, amino, optionally-substituted alkyl and a ligand;

n is greater than 1; and

i is greater than 1.

2. (currently amended) A compound in accordance with claim 1, wherein:

Y is a member selected from the group consisting of hydrogen, optionally-substituted C<sub>1</sub>-C<sub>4</sub> alkyl, optionally-substituted C<sub>5</sub>-C<sub>6</sub> cycloalkyl and optionally-substituted phenyl;

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X is a member selected from the group consisting of optionally-substituted amino, oxygen and sulfur;

R<sup>2</sup> is a member selected from the group consisting of hydrogen, C<sub>6</sub>-C<sub>26</sub> alkyl and C<sub>6</sub>-C<sub>26</sub> alkenyl; n and i, added together, have a sum of about 40 to about 250.

3. (currently amended) A compound in accordance with claim 1, wherein:

Y is a member selected from the group consisting of hydrogen, optionally substituted C1-C4 alkyl, optionally substituted C5-C6 cycloalkyl and optionally substituted phenyl;

X is optionally-substituted amino;

R<sup>2</sup> is a member selected from the group consisting of C<sub>6</sub>-C<sub>26</sub> alkyl and C<sub>6</sub>-C<sub>26</sub> alkenyl; n and i added together have a sum of about 40 to about 250.

4. (currently amended) A compound in accordance with claim 1, wherein:

Y is a member selected from the group consisting of hydrogen, optionally substituted C1-C4 alkyl, optionally-substituted C5-C6 cycloalkyl and optionally-substituted phenyl;

X is a carbon single bond;

R<sup>2</sup> is a member selected from the group consisting of dialkylglycerolyl, dialkenylglycerolyl, diacylglycerolyl, 1,2-diacyl-sn-glycero-3-phosphoethenyl, 1,2-dialkoxy-3-aminopropanyl and 1,2-diacyloxy-3-aminopropanyl;

n and i added together have a sum of about 40 to about 250.

5. (currently amended) A compound in accordance with claim 1, wherein:

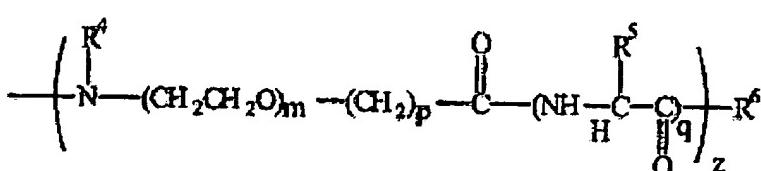
Y is a member selected from the group consisting of hydrogen, optionally substituted C<sub>1</sub>-C<sub>4</sub> alkyl, optionally-substituted C5-C6 cycloalkyl and optionally-substituted phenyl;

X is a carbon single bond;

R<sup>2</sup> is a member selected from the group consisting of dialkylglycerolyl, dialkenylglycerolyl, diacylglycerolyl, 1,2-dialkoxy-3-aminopropanyl and 1,2-diacyloxy-3-aminopropanyl; and n and i, added together, have a sum of about 40 to about 250.

6. (original) A compound in accordance with claim 1, wherein:

R<sup>3</sup> is a ligand, said ligand being a member selected from the group consisting of a lipid, polyethylene glycol and a compound of the formula



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wherein:

R<sup>4</sup> is a member selected from the group consisting of hydrogen and alkyl;

R is a member of the group selected from hydrogen, optionally substituted alkyl, optionally-substituted aryl and a side chain of an amino acid;

R<sup>6</sup> is a member selected from the group consisting of hydrogen, halogen, hydroxy, alkoxy, mercapto, hydrazino, amino and NR<sup>7</sup>R<sup>8</sup>, wherein R<sup>7</sup> and R<sup>8</sup> are independently hydrogen or alkyl; z is 4 to 80; m is 2 to 6;

p is 1 to 4; and q is 0 or 1.

7. (original) A compound in accordance with claim 1, wherein:

R is a member selected from the group consisting of C<sub>10</sub>-C<sub>18</sub> alkyl and C<sub>10</sub>-C<sub>18</sub> alkenyl.

8. (original) A compound in accordance with claim 1, wherein:

R<sup>2</sup> is a member selected from the group consisting of dialkylglycerolyl and dialkenylglycerolyl, wherein said dialkyl groups are C<sub>10</sub>-C<sub>18</sub> dialkyl and said dialkenyl groups are C<sub>10</sub>-C<sub>18</sub> dialkenyl.

9. (original) A compound in accordance with claim 1, wherein:

R<sup>2</sup> is a member selected from the group consisting of diacylglycerolyl and 1,2-diacyl-sn-glycero-3-phosphoethylenyl, wherein said diacyl groups are C<sub>10</sub>-C<sub>18</sub> diacyl.

10. (original) A compound in accordance with claim 1, wherein:

R<sup>2</sup> is a member selected from the group consisting of C<sub>10</sub> alkyl and C<sub>10</sub> alkenyl.

11. (original) A compound in accordance with claim 1, wherein:

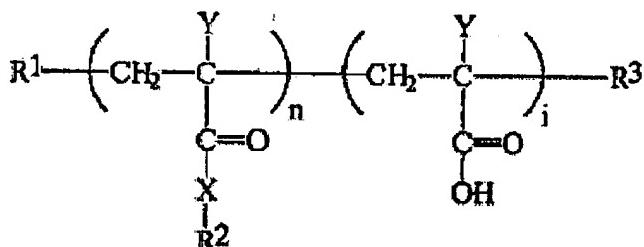
R<sup>2</sup> is a member selected from the group consisting of dialkylglycerolyl and dialkenylglycerolyl, wherein said dialkyl groups are C<sub>10</sub> dialkyl and said dialkenyl groups are C<sub>10</sub> dialkenyl.

12. (original) A compound in accordance with claim 1, wherein:

R<sup>2</sup> is a member selected from the group consisting of diacylglycerolyl and 1,2-diacyl-sn-glycero-3-phosphoethylenyl, wherein said diacyl groups are C<sub>10</sub> acyl.

13. (currently amended) A pH-sensitive liposome, said liposome comprising a lipid and a compound of the formula

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wherein:

$\text{R}^1$  is a member selected from the group consisting of hydrogen, hydroxyl, amino, optionally-substituted alkyl and a ligand;

$\text{Y}$  is a member selected from the group consisting of hydrogen, optionallysubstituted alkyl, optionally-substituted cycloalkyl, optionally-substituted aryl and optionally-substituted heteroaryl;

$\text{X}$  is a member selected from the group consisting of optionally-substituted amino, oxygen, sulfur a carbon single bond;

$\text{R}_2$  is a member selected from the group consisting of hydrogen,  $\text{C}_6\text{-C}_{26}$  alkyl,  $\text{C}_6\text{-C}_{26}$  alkenyl, dialkylglycerolyl, dialkenylglycerolyl, diacylglycerolyl, 1,2-diacyl-sn-glycero-3-phosphoethenyl, 1,2-dialkoxy-3-aminopropanyl and 1,2-diacyloxy-3-aminopropanyl;

$\text{R}^3$  is a member selected from the group consisting of hydrogen, hydroxyl, amino, optionally-substituted alkyl and a ligand;

$n$  is greater than 1; and

$i$  is greater than 1.

14. (original) A pH-sensitive liposome in accordance with claim 13 wherein said liposome is fusogenic.

15. (currently amended) A pH-sensitive liposome in accordance with claim 13 wherein said lipid is a member selected from the group consisting of phosphoglycerides, sphingolipids, phosphatidylcholine, phosphatidylethanolamine, ~~anionic lipids, cationic lipids, noncationic lipids, alternative cationic lipids, neutral lipids, lipolyamines, and cholesterol-based lipids.~~

16. (original) A pH-sensitive liposome in accordance with claim 15 wherein said lipid is a phosphatidylcholine.

17. (original) A pH-sensitive liposome in accordance with claim 16 wherein said phosphatidylcholine lipid is a member selected from the group consisting of

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distearoylphosphatidylcholine, dipalmitoylphosphatidylcholine, dimyristoylphosphatidylcholine, dilauroylphosphatidylcholine, dioleylphosphatidylcholine, hydrogenated egg phosphatidylcholine, soy phosphatidylcholine, hydrogenated soy phosphatidylcholine, and egg phosphatidylcholine.

18. (original) A pH-sensitive liposome in accordance with claim 13 wherein said lipid is a mixture of egg phosphatidylcholine, dimyristoylphosphatidylcholine, dipalmitoylphosphatidylcholine and distearoylphosphatidylcholine.

19. (original) A pH-sensitive liposome in accordance with claim 13 further comprising cholesterol

20. (original) A pH-sensitive liposome in accordance with claim 19 wherein said lipid is egg phosphatidylcholine.

21. (original) A pH-sensitive liposome in accordance with claim 13 further comprising a bilayer stabilizing component.

22. (currently amended) A pH-sensitive liposome in accordance with claim 13 wherein said bilayer stabilizing component is a member selected from the group consisting of lipids, lipid derivatives, detergents, proteins, peptides, polyethylene glycol and N-(omega-N'-acetoxy-octa(14'amino-3',6',9',12'-tetraoxatetradecanoyl)) (ATTA). ~~ATTA~~

23. (original) A pH-sensitive liposome in accordance with claim 22 wherein said polyethylene glycol has a molecular weight ranging from about 200 to 10,000.

24. (original) A pH-sensitive liposome in accordance with claim 22 wherein said ATTA has a molecular weight ranging from about 200 to 10,000.

25. (original) A pH-sensitive liposome in accordance with claim 22 wherein said polyethylene glycol has a molecular weight ranging from about 2,000 to 6,000.

26. (original) A pH-sensitive liposome in accordance with claim 22 wherein said ATTA has a molecular weight ranging from about 2,000 to 6,000.

27. (original) A pH-sensitive liposome in accordance with claim 13 wherein said compound is present at a concentration ranging from about 1 weight percent to about 22 weight percent of said lipid

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28. (original) A pH-sensitive liposome in accordance with claim 27 wherein said compound is present at a concentration ranging from about 2 percent to about 20 percent of lipid in a weight to weight ratio.

29. (original) A pH-sensitive liposome in accordance with claim 27 wherein said compound is present at a concentration ranging from about 8 percent to about 10 percent of lipid.

30. (original) A pH-sensitive liposome in accordance with claim 19 wherein said cholesterol is present at a concentration ranging from about 0.02 mole percent to about 50 mole percent.

31. (original) A pH-sensitive liposome in accordance with claim 19 wherein said cholesterol is present at a concentration ranging from about 40 mole percent to about 45 mole percent.

32. (original) A pH-sensitive liposome in accordance with claim 13 wherein said liposome becomes permeable, unstable or fusogenic at a rate which can be controlled by pH

33. A pH-sensitive liposome in accordance with claim 13 wherein said liposome becomes destabilized at a rate which can be controlled by pH.

34. (original) A pH-sensitive liposome in accordance with claim 13 wherein said liposome becomes fusogenic at a rate which can be varied over a pH range of about 3 to about 10.

35. (original) A pH-sensitive liposome in accordance with claim 13 wherein said liposome becomes destabilized at a rate which can be controlled by varying Y

36. (original) A pH-sensitive liposome in accordance with claim 35 wherein Y is different in every other monomer n.

37. (original) A pH-sensitive liposome in accordance with claim 35 wherein Y is different in every other monomer i.

38. (currently amended) A method for delivering a therapeutic compound to a target cell comprising administering to a host containing said target cell a pH-sensitive liposome, said pH-sensitive liposome comprising:

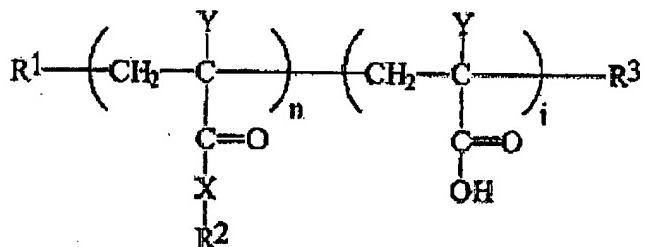
a lipid;

a compound of the formula

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39. (currently amended) A method in accordance with claim 38 further comprising a bilayer stabilizing component, wherein said bilayer stabilizing component is a member selected from the group consisting of lipids, lipid derivatives, detergents, proteins, peptides, polyethylene glycol and ATTA.

40. (original) A method in accordance with claim 38 wherein said liposome further comprises cholesterol.

41. (currently amended) A method in accordance with claim 38 wherein said liposome is fusogenic over a pH range from about 4 to about 7.

42. (original) A method in accordance with claim 38 wherein said liposome is administered intravenously.

43. (original) A method in accordance with claim 38 wherein said liposome is administered parenterally.

44. (original) A method in accordance with claim 38 wherein said liposome administered to said host is unilamellar.

45. (original) A method in accordance with claim 44 wherein said unilamellar liposome has a mean diameter of 0.05 microns to 0.45 microns.

46. (original) A method in accordance with claim 45 wherein said unilamellar liposome has a mean diameter of 0.05 microns to 0.2 microns.